Nephro-Urology Monthly
Volume 18 · Issue 2 · e169008

OPEN PEER REVIEW

Factors Associated with Upgrading of Pathological ISUP Grading Following Radical Prostatectomy: A Retrospective Cohort Study

Reza Shahrokhi-Damavand, Emad Moaied Abedi, Samaneh Esmaeili, Ardalan Akhavan Tavakoli, Shahab Aali, Ehsan Kazemnezhad Leili

SUBMITTED	REVISED	ACCEPTED	DOI
13 Dec 2025	30 Apr 2026	22 May 2026	10.5812/numonthly-169008

About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

More about open peer review: brieflands.com/knowledgebase/opr

Contents

1 **Original submission** Referee 1, Referee 2, Associate Editor, Editor-in-Chief 2
2 **Revision 1** Referee 1, Referee 2, Associate Editor, Editor-in-Chief 6
Authors' reply to reviewers 7
Reviewer and editor comments 13
3 **Revision 2** Referee 2, Referee 1, Associate Editor, Editor-in-Chief 15
Authors' reply to reviewers 16
Reviewer and editor comments 19

1 Original submission

4 comments · 30 Dec 2025 – 12 Feb 2026

Referee 1 Reviewer

MAJOR REVISION 30 Dec 2025

Dear AE,
Thank you for the invitation.
This manuscript addresses an important and clinically relevant issue in prostate cancer management: discordance between biopsy-based ISUP grading and final radical prostatectomy pathology.
The following are concerns and suggestions:
1-The study is described as “descriptive-analytic” and elsewhere as “retrospective analytical”. Please standardize the terminology and clearly state that this is a retrospective cohort study.
2-No sample size calculation or power analysis is provided. Given the relatively small cohort (n=110) and multiple variables examined, the study may be underpowered to detect associations—particularly for MRI and pathological features.
3-The manuscript should clarify:

*Whether MRI was performed before biopsy in all patients

*Whether radiologists were blinded to pathology
4-Several grammatical and stylistic issues require editing.
For example:
“patients underwent RP” → “patients who underwent RP”
“Date Analysis” → “Data Analysis”
“are showed” → “are shown”
5-Some sentences lack references (for example, the first sentence of the Background). All sentences quoted from other articles must have references at the end.
6-The conclusions are generally supported by the data but should be rephrased to:
*Avoid overgeneralization
*Highlight the need for prospective validation
7-In all tables, abbreviations must be explained in a legend.
8-The Background and Discussion sections repeat identical concepts.
9-P values are sometimes reported without specifying the test used.
10-Some references are outdated despite the availability of newer ISUP-based studies.

Referee 2 Reviewer

MAJOR REVISION 10 Feb 2026

Dear Authors,
Thank you for submitting this interesting paper. The clinical issue you are examining—identifying factors associated with ISUP grade upgrading from biopsy to radical prostatectomy—is very important for risk assessment and treatment decisions in prostate cancer. However, in its current form, the study has some major methodological and statistical problems that require substantial changes before it can be considered for publication.

1. Study design and internal validity
1.1. Incorrect label: Currently, the study is described as “descriptive-analytic” and, in some places, appears to be almost a cross-sectional study. In fact, your study is a retrospective cohort study of men with biopsy-confirmed prostate cancer who subsequently underwent radical prostatectomy, with ISUP grade upgrading

between biopsy and the surgical specimen as the outcome. This incorrect label is not merely a matter of wording; it affects how the study should be described, analyzed, and reported.

• You need to clearly identify the design as a retrospective cohort study throughout the paper (in the Title, Abstract, Methods, and Discussion).

• I strongly suggest following the STROBE guideline for reporting cohort studies. In particular, the Methods section should clearly describe:

o The study population and eligibility criteria: how patients were identified, the inclusion and exclusion criteria, and the exact time period.

o The starting point and follow-up: biopsy as the starting point and the time until RP as the follow-up period. The wide range of this interval (24–655 days) should be described and discussed later as a possible source of bias.

o Exposure variables: PSA, f/tPSA, prostate volume, PSAD, MRI results, biopsy ISUP grade, etc., with clear information on when and how they were measured.

o Outcome definition: ISUP grade upgrading, including how downgrading was handled in the analysis (e.g., excluded, grouped with no upgrading, or analyzed separately).

1.2. Internal validity, bias, and confounding:

• Selection bias: Your cohort includes only patients who underwent radical prostatectomy. Patients on active surveillance or receiving radiotherapy are excluded. This limits the target population to surgical patients and could bias the associations if the choice of surgery is related to unmeasured factors (e.g., comorbidities, patient preferences, or physician judgment).

• Information bias: ISUP grading of biopsy and RP specimens can vary between observers. You discuss this in the Discussion, but the Methods section provides no information on standardization, double-checking, or central review. Even if these measures were not possible, this limitation should be clearly stated with regard to possible misclassification.

• Confounding: Some important potential confounders are not considered. For example, the biopsy method (systematic or MRI-targeted), number and locations of cores, year of the procedure (to account for changes in practice), and center or pathologist experience could affect both the likelihood of upgrading and the exposures. At a minimum, discuss this; preferably, if the data allow, include some of these factors in the analysis.

2. Statistical analysis and modeling

2.1. Sample Size and Statistical Power: The final sample (n = 110) is quite small for multivariable logistic regression, especially with many initial candidate predictors. The lack of significant findings for many known predictors (PSA, PSAD, MRI) might reflect low power rather than a true absence of association, and this should be stated more clearly.

2.2. Variable selection strategy: You state that variables with $p<0.25$ in the univariate analysis were included in the multivariable model. This “univariate screening” is no longer widely recommended, as it can produce unstable estimates and biased results, especially with few outcome events (47 upgrades).

I suggest:

1. Choose a set of clinically and biologically relevant covariates in advance (e.g., age, PSA, f/tPSA, PSAD, biopsy ISUP grade, MRI PI-RADS, prostate volume).

2. Fit a multivariable model based on this rationale rather than on univariate p-values.

3. With a modest number of events, consider limiting the number of predictors or using penalized methods (e.g., ridge or LASSO) if you want to include more variables.

2.3. Handling of continuous variables: Dichotomizing f/tPSA at 10% and other variables at arbitrary cutoffs (e.g., PSA <10 vs. ≥10, PSAD <0.15 vs. ≥0.15) loses information and power and creates artificial thresholds.

1. It would be better to model f/tPSA, PSA, PSAD, and prostate volume as continuous variables.

2. Check for nonlinearity using, for example, restricted cubic splines, or at least assess whether a linear relationship is appropriate.
3. If retaining cutoffs for clinical convenience, justify them (using guidelines or previous studies) and, if possible, show that the results hold with alternative categories.
2.4. Missing data: The paper does not describe how missing data were handled. You state that some patients were excluded because of incomplete records, but it is unclear whether any variables are missing among the 110 patients (e.g., MRI).
1. Report the extent and pattern of missing data for each key variable.
2. If a complete-case analysis was used, state this clearly and discuss possible bias.
3. If there is a substantial amount of missing data, consider multiple imputation as a sensitivity analysis.
2.5. Model reporting and interpretation
1. Table 3 is mostly good, but the interpretation in the text is sometimes incorrect. For example, stating "with an increase of one unit in f/tPSA ratio, probability of upgrading decreases by 1.30 units" is incorrect. An odds ratio of 0.27 means that, for each unit increase in f/tPSA, the odds of upgrading are multiplied by 0.27 (a 73% reduction). Please correct such passages carefully.
2. Report all odds ratios with 95% confidence intervals, and report p-values consistently (e.g., p=0.004, not p>0.004).
3. It would be useful to report basic model performance (e.g., the c-statistic for discrimination and a brief note on calibration).
3. Interpretation of findings and strength of conclusions
Your main findings—that low f/tPSA and ISUP grade 1 on biopsy are associated with a higher risk of upgrading—are reasonable and consistent with some previous literature. However, the evidence is sometimes overstated in the Discussion and Conclusion.
• Given the retrospective observational design, it would be better to use "factors associated with upgrading" rather than "predictive factors" in a strong causal or prognostic sense.
• Greater caution is needed when suggesting, based on your data, that active surveillance "may not be suitable" for some ISUP 1 patients. Your cohort includes only RP patients, not patients on surveillance, so you cannot compare outcomes directly.
• The variable biopsy-to-surgery interval, lack of central pathology review, and absence of some confounders all limit causal interpretation. These issues are mentioned but could be emphasized more strongly in the Limitations section.
4. Reporting quality, structure, and clarity
4.1. Consistency: In some places, you refer to "three referral centers," and in others, to "two hospitals." Make sure the number and type of institutions are consistent and clear.
4.2. Flow diagram: You refer to Figure 1 for patient selection, but it is not visible in the text. A clear flowchart is needed, with numbers at each step (initial patients, excluded patients with reasons, and the final sample).
4.3. Tables:
4.3.1. Table 1 combines continuous and categorical variables; consider separating them or clearly indicating which values are means ± SD and which are n (%).
4.3.2. For skewed distributions, such as PSA, medians and IQRs are preferable to means and SDs.
4.3.3. Define all abbreviations in footnotes or a list.
5. Language and style:
5.1. Some sentences are long; simplify them for clarity.
5.2. Correct minor typos (e.g., "Date Analysis" instead of "Data Analysis").
5.3. Use a consistent term for ISUP (e.g., "ISUP Grade Group" or "ISUP grade").

Final Note
In short, the paper addresses an important clinical question. However, the current version has major issues

that need to be addressed to strengthen it. If the authors address these carefully, I think the paper could contribute useful information to the literature and may be suitable for publication in NUM.
Kind regards,

Associate Editor

MAJOR REVISION 12 Feb 2026

Dear EIC,
Thank you for the invitation.
The reviewers and I have now completed the review process. We found this work to be of interest and suitable for publication pending major revisions.
The reviewers have provided constructive feedback to help improve the clarity and presentation of the manuscript. I encourage the authors to carefully address each of the reviewers' comments and submit a revised version of the manuscript.

Sincerely,
Associate Editor, Nephro-Urology Monthly

Editor-in-Chief

MAJOR REVISION 12 Feb 2026

Major Revision

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor,
I am very grateful that you gave us a chance to be reviewed in your privileged journal and I wish to express my appreciation to the editor for the time and precise opinions.
I have revised the manuscript on the base of the comments and all the revisions and edits, which has been made, are highlighted in yellow in manuscript body.

Reviewer 0:
We would like to extend our sincere gratitude for your insightful comments, which have helped us significantly improve the paper.

1. Study design and internal validity
1.1. Wrong label: Right now, the study is called “descriptive-analytic” and, in some places, it seems almost like a cross-sectional study. Actually, what you did is a retrospective cohort study: men with prostate cancer confirmed by biopsy who then had radical prostatectomy, and the outcome is the upgrading of ISUP grade between biopsy and the surgical specimen. This wrong label is not just about words; it changes how the study should be taught, analyzed, and reported.
The type of study in the text and title was corrected.

• You need to clearly change the design to retrospective cohort throughout the paper (in Title, Abstract, Methods, Discussion). The type of study in the text and title was corrected.
• I really suggest following the STROBE guideline for cohort studies in reporting. Especially, the

Methods section should say clearly:
o The study base and who can be included: how patients were found, what inclusion and exclusion rules, and the exact time period.
o Time start and follow-up: biopsy as the beginning, and the time until RP as follow-up. The big range of this time (24–655 days) should be described and talked about later as a possible bias source. This factor evaluated as an independent variable and the results showed that it had no statistically significant effect on upgrading.
o Exposure variables: PSA, f/tPSA, prostate volume, PSAD, MRI results, biopsy ISUP grade, etc., with clear info on when and how they were measured.
o Outcome definition: upgrading of ISUP grade, including how you dealt with downgrading in analysis (like excluded, put together with no upgrading, or analyzed apart).
STROBE guideline was followed in Method section and all correction was made with more description.

1.2. Internal validity, bias, and confounding:
• Selection bias: Your group only has patients who underwent radical prostatectomy. Those on active surveillance or radiotherapy are out. This makes the target population only surgical patients and could bias the links if surgery choice relates to things not measured (like other health issues, patient choice, doctor opinion).
• Information bias: ISUP grading on biopsy and RP can vary between observers. You talk about this in Discussion, but Methods has no info on standardization, double-checking, or central review. Even if not possible, this limit should be said clearly to avoid possible misclassification.

• Confounding: Some important possible confounders are not looked at. For example, the biopsy method (systematic or MRI-targeted), number and places of cores, year of procedure (for changes in practice), and center or pathologist experience could affect both the upgrading chance and the exposures. At least, discuss this; better if data allow, add some to the analysis.
All these factors were discussed in method and limitation. Biopsy technique was relatively homogeneous across patients, as all patients underwent systematic TRUS biopsy.

2. Statistical analysis and modelling
2.1. Sample Size and Statistical Power: The final sample (n = 110) is quite small for multivariable logistic regression, especially with many candidate predictors at the start. No significant findings for many known predictors (PSA, PSAD, MRI) might be from low power, not a real no association, and this should be said more clearly. We excluded variables with p<0.25 in univariate: PSA, PSAD, MRI and PV for increasing the power of the study.

2.2. Variable selection strategy: You say variables with p<0.25 in univariate were put in the multivariable model. This “univariate screening” is now not recommended much, as it can make unstable estimates and biased results, especially with few outcome events (47 upgrades).
I suggest:
1. Choose a set of clinically and biologically sensible covariates before (like age, PSA, f/tPSA, PSAD, biopsy ISUP grade, MRI PI-RADS, prostate volume).
2. Fit a multivariable model for this reason, not univariate p-values.
3. With modest events, maybe limit predictors or use penalized methods (like ridge or LASSO) if you want more variables.
Your suggestion is very correct, but I need to explain how to choose the implementation method. If there were no sample size limitation, there would be no need to use the p-value cutoff for variable inclusion in the multivariable model. In studies with small sample sizes, such as our study, this method is used to increase the power of the study and analyses. In fact, following the esteemed referee's suggestion will increase the input variables and reduce the efficiency of the model.
To make the execution method and the selection of variables clearer, additional explanations were provided in the Method and Results sections.

2.3. Handling of continuous variables: Cutting f/tPSA at 10% and others at random points (like PSA <10 vs ≥10, PSAD <0.15 vs ≥0.15) loses info and power, and makes fake thresholds.
1. Better to model f/tPSA, PSA, PSAD, prostate volume as continuous.
2. Check non-linearity with, say, restricted cubic splines or at least see if linear is ok.
3. If keeping cuts for clinical ease, justify them (from guidelines, past studies) and show results hold with other categories if possible.

On the base of evidence in EAU guideline, PSA < 10 ng/mL is in low-risk groups for biochemical recurrence of localized and locally-advanced prostate cancer and those with PSA above 10 ng/mL located in intermediate-risk group. So, this cut-off for PSA can change the risk group.

The higher the PSAD, the more likely clinically significant PCa is present; in particular in smaller prostates when a PSA-D cut-off of 0.15 ng/mL/cc was applied. Several studies found a PSAD over 0.1-0.15 ng/mL/cc predictive of PCa.
In a multi-centre retrospective cohort of 1,476 men with PIRADS 3 lesions and a prevalence of 18.5% of ISUP GG ≥ 2 cancer, age, prior negative biopsy and PSA-D were significant independent predictors of the presence of ISUP GG ≥ 2 cancer at subsequent systematic and targeted biopsy. Applying a PSA-D cut-off of 0.15 ng/mL/cc, 817 biopsy procedures (58.4%) would have been avoided at the cost of missing ISUP GG ≥ 2 cancer in 91 men (6.5%); ISUP GG 1 cancer would not have been detected in 115 men (8.2%)

- Maggi, M., et al. Prostate Imaging Reporting and Data System 3 Category Cases at Multiparametric Magnetic Resonance for Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol Focus, 2020. 6: 463.
- Nordstrom, T., et al. Prostate-specific antigen (PSA) density in the diagnostic algorithm of prostate cancer. Prostate Cancer Prostatic Dis, 2018. 21: 57.
- Denijs, F.B., et al. Risk calculators for the detection of prostate cancer: a systematic review. Prostate Cancer Prostatic Dis, 2024. 27: 544.
- Sigle, A., et al. Prediction of Significant Prostate Cancer in Equivocal Magnetic Resonance Imaging Lesions: A High-volume International Multicenter Study. Eur Urol Focus, 2023. 9: 606.

Different cutoffs were recommended for f/tPSA. On the base of a study by Erol et al., according to sensitivity and specificity f/tPSA cutoff points were determined to be 10%, 15%, 15%, and 10% in 50–59 years, 60–69 years, >70 years, and all ages categories, respectively, in the diagnosis of prostate cancer in patients with initial PSA level of 4–10 ng/mL. As, the risk of prostate cancer in lower level of f/tPSA is higher, we considered 10% in our study.

- Erol B, Gulpinar MT, Bozdogan G, et al. The cutoff level of free/total prostate specific antigen (f/t PSA) ratios in the diagnosis of prostate cancer: A validation study on a Turkish patient population in different age categories. The Kaohsiung Journal of Medical Sciences. 2014; 30(11): 545-550.

2.4. Missing data: The paper does not say how missing data is handled. You say some patients were excluded for incomplete records, but not clear if in the 110, some variables are missing (like MRI).
1. Report how much and the pattern of missing for each key variable.
2. If used in a complete case, say it clearly, and discuss possible bias.
3. If missing is a lot, think multiple imputation for sensitivity.
Missing data was explained in a separate section under heading “Missing data” at the end of method.

2.5. Model reporting and interpretation
1. Table 3 is mostly good, but the text interpretation is sometimes wrong. For example, saying “with an increase of one unit in f/tPSA ratio, probability of upgrading decreases by 1.30 units” is not right. An odds ratio of 0.27 means that for each unit increase in f/tPSA, the odds of upgrading multiply by 0.27 (reduced 73%). Please fix such parts carefully.
2. Report all odds ratios with 95% confidence intervals, and p-values in the same way (like p=0.004, not p>0.004).
3. Good to report some basic model performance (like c-statistic for discrimination, and a short note on calibration).
Corrections were made to the text.

3. Interpretation of findings and strength of conclusions
Your main results—that low f/tPSA and ISUP grade 1 on biopsy link to higher upgrading risk—are reasonable and match some past literature. But in the Discussion and Conclusion, sometimes the evidence is overstated.
• With retrospective observational design, better to say “factors associated with upgrading” than “predictive factors” in a strong causal or prognostic way. Corrections were made to the title and text.
• Suggesting active surveillance “may not be suitable” for some ISUP 1 patients, based on your data should be more careful. Your group is only RP patients, not surveillance ones, so you cannot compare outcomes directly. This sentence was deleted from manuscript body.
• The varying biopsy-to-surgery time, no central pathology, and missing some confounders all limit the causal view. These are said, but could be stronger in Limitations. This factor evaluated as an independent variable and the results showed that it had no statistically significant effect on upgrading.

4. Reporting quality, structure, and clarity
4.1. Consistency: Sometimes “three referral centers,” other places “two hospitals.” Make sure same and clear on the number and type. There was a typo and only two hospitals were surveyed.
4.2. Flow diagram: You point to Figure 1 for selection, but not seen in the text. Need a clear flowchart with numbers at each step (initial, excluded with reasons, final). Figure 1 cited in the end of first paragraph of method and attached as a separated file in JPG format (according to journal rules). Only 123 patients were enrolled in the study, of whom 13 were excluded for reasons explained in the text, and analyses were performed on 110 patients. All steps in the flowchart are indicated by patient numbers.
4.3. Tables:
4.3.1. Table 1 mixes continuous and categorical; maybe separate or mark clear which are means ± SD, which n (%). The data distribution is specified in all rows.
4.3.2. For skewed distributions like PSA, medians and IQR are better than means and SD. Corrections were made.
4.3.3. Define all abbreviations in footnotes or a list. Some definitions were added to the list of abbreviations at the end of the article.
5. Language and style:
5.1. Some sentences are long; simplify for clarity. Corrections were made and some sentences deleted.
5.2. Small typos (like “Date Analysis” not “Data Analysis”) fix. Grammar and spelling corrections were made throughout the text.
5.3. Keep the same term for ISUP (like “ISUP Grade Group” or “ISUP grade”). Corrections were made.

Final Note
In short, the paper looks at an important clinical question. But the current has big issues to fix for its strength. If authors address these carefully, I think it could add useful information to the literature and maybe suit for publication in NUM. We sincerely appreciate all your valuable comments and suggestions, which helped us in improving the quality of the manuscript.

Reviewer 1:
We would like to express our appreciation for your precious and valuable comments, which helped us in improving the quality of the manuscript and we are very glad that you have paid so much attention toward our work.

1-The study is described as “descriptive-analytic” and elsewhere as “retrospective analytical”. Please standardize terminology and clearly state that this is a retrospective cohort study. The type of study in the text and title was corrected.

2-No sample size calculation or power analysis is provided. Given the relatively small cohort (n=110) and multiple variables examined, the study may be underpowered to detect associations —particularly for MRI and pathological features.
The small sample size was one of the main limitations of our study, and due to the shortcomings of the patient records, it was not possible to increase the sample size. This point was mentioned in the limitations section at the end of the study.

3-The manuscript should clarify:
*Whether MRI was performed before biopsy in all patients. All MRIs were performed before biopsies and this was added in methods.
*Whether radiologists were blinded to pathology. Yes, as mentioned, MRIs were performed before biopsies.
More details are provided in the method section.

4-Several grammatical and stylistic issues require editing. for example: “patients underwent RP” → “patients who underwent RP”
“Date Analysis” → “Data Analysis” “are showed” → “are shown”
Grammar and spelling corrections were made throughout the text.

5-Some sentences lack references (for example first sentence of Background). All sentences quoted from other articles must have references at the end of themselves.
Since many consecutive sentences are quoted from the same reference, the reference is given at the end of the last sentence to avoid repetition.

6-The conclusions are generally supported by the data, but should be rephrased to:
*Avoid overgeneralization
*Highlight need for prospective validation
Corrections were made.

7-In all Tables, the abbreviated words must be explained, in a Legend. Corrections were made.

8-The Background and Discussion sections repeat identical concepts. The background and discussion text were made more concise and repetitive sentences were removed.

9-P values are sometimes reported without specifying the test used. All tests used are mentioned in the “Data Analysis” section and tables.

10-Some references are outdated despite availability of newer ISUP-based studies. Some old references were replaced by new ones.

Kind regards,
Samaneh Esmaeili
Corresponding author

2 Revision 1

4 comments · 8 Jun 2026 – 23 Jun 2026

Referee 1 Reviewer

MAJOR REVISION 8 Jun 2026

Dear AE,
Thank you for the invitation.
This manuscript investigates predictors of ISUP grade upgrading between prostate biopsy and radical prostatectomy specimens. The topic is clinically relevant because discordance between biopsy and final pathology may influence treatment decisions, particularly in patients initially classified as having low-risk disease. However, the manuscript contains several structural, methodological, and writing deficiencies that should be addressed before it can be considered for publication:

1-Some sentences lack references. All sentences quoted from other articles must have references at the end. For example, the sentence below:

"Clinically, many patients who present with grade 1 pathology from PB may not be considered ....."

2-Although the study is described as a retrospective cohort, the manuscript does not clearly explain:

how patients were identified (registry, hospital database, pathology archive)
whether consecutive patients were included
whether selection bias was minimized.
3-MRI findings were available for only 102 of 110 patients, and these data were analyzed only descriptively. However:

*the effect of missing MRI data on the analysis is not addressed
*no sensitivity analysis was performed.

4-The introduction contains several structural problems:

*repetitive explanation of Gleason scoring and ISUP grading
*limited emphasis on the specific knowledge gap addressed by the study
*insufficient discussion of recent literature using ISUP grading groups.
5-The manuscript contains numerous grammatical and stylistic problems that reduce clarity.

6-Units for variables should be standardized.
7-In Table 2, the number of MRI cases analyzed is not clearly indicated in the table header.
8-The discussion contains excessive narrative description and repetition of earlier findings. A clearer comparison with key studies on ISUP upgrading rates would improve it.
9-While some references are recent, it would strengthen the manuscript to include more recent studies or systematic reviews to reinforce the findings and claims made in the discussion.
10-The figure legend should be written more clearly.

Referee 2 Reviewer

ACCEPT 11 Jun 2026

Dear Authors,
Thank you for the careful revision and for answering all comments in detail. I can clearly see that the manuscript is much better now.
The study design is properly explained as a retrospective cohort; missing methodological points were added, reporting mistakes were fixed, and limitations are now discussed openly. The interpretation of findings is also

more balanced and fits the observational design. These are all meaningful improvements.
The main concerns from the earlier review round were addressed well. Some weaknesses remain, of course—small sample size, retrospective nature, possible residual confounding—but these are fairly acknowledged and, I think, do not detract from the value of the findings.
Decision
In my view, the manuscript has improved enough and is ready for publication in NUM.
Kind Regards,

Associate Editor

MAJOR REVISION 13 Jun 2026

Dear EIC,
I thank the authors and express my appreciation to the researchers. The manuscript presents valuable research. However, some revisions are needed. The authors should revise it based on the reviewers' comments. Minor changes should also be made to the abstract:
1- The abstract does not specify what constitutes "upgrading."
Does any increase (e.g., ISUP 1 to 2) count, or only "significant" upgrading (e.g., ISUP 1 to ≥ 3)?
Define "upgrading" clearly in the Methods section.
2-A summary of the statistical analysis results should be included in the Results section of the abstract.
3-In the Results section, the manuscript states: "Age, PSA, PSA density (PSAD)… were not significantly associated with ISUP upgrading (P>0.05)."

However, in the next sentence, the manuscript states that ISUP Grade 1 on biopsy was significantly associated with upgrading (*P*=0.002 P=0.002).

Critique: "ISUP grade" is a pathological finding. The manuscript cannot say "pathological findings were not significant" and then list a pathological finding (ISUP 1) as significant. This is a contradiction.
4-The conclusion is somewhat generic. Instead of saying "should be taken into account," specify how.

Editor-in-Chief

MAJOR REVISION 23 Jun 2026

Major Revision

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor,
I wish to express my appreciation to the editor for the time and precise opinions. I have revised the manuscript on the base of the comments and all the revisions and edits, which has been made, are highlighted in yellow in manuscript body. I hope that these changes to the manuscript will facilitate the decision to publish this study in your journal.

Reviewer 3:
We would like to thank you for taking the time and effort to review the manuscript. We sincerely appreciate all your valuable comments and suggestions, which helped us in improving the quality of the manuscript.

1-Some sentences lack references. All sentences quoted from other articles must have references at the end of themselves.
FOR example, below sentence:
Clinically, many patients who present with grade 1 pathology from PB may not be considered ....
The reference of the relevant sentences was mentioned. Sometimes more than one sentence contains one or more similar references, so to avoid repetition, the number of references is mentioned in the last sentence.

2-Although the study is described as a retrospective cohort, the manuscript does not clearly explain:
how patients were identified (registry, hospital database, pathology archive)
whether consecutive patients were included
whether selection bias was minimized.
Detailed explanation added in the method section.

3-MRI findings were available for only 102 of 110 patients, and these data were analyzed only descriptively. However:
*the effect of missing MRI data on analysis is not addressed
*no sensitivity analysis was performed.
Explanations regarding missing data were given in the relevant section, and this issue was also mentioned more clearly in the design limitations.

4-The introduction contains several structural problems:
*repetitive explanation of Gleason scoring and ISUP grading
*limited emphasis on the specific knowledge gap addressed by the study
*insufficient discussion of recent literature using ISUP grading groups.
Correction has been made in Introduction. The knowledge gap addressed by the present study was clarified by emphasizing the limited data regarding predictors of ISUP grade upgrading in patients undergoing radical prostatectomy, particularly in studies using the contemporary ISUP grading classification.

5-The manuscript contains numerous grammatical and stylistic problems that reduce clarity. The manuscript checked again by an English expert and some corrections have been made in the text.

6-Units for variables should be standardized. Correction has been made.

7-In Table 2, The number of MRI cases analyzed is not clearly indicated in the table header. Correction has been made.

8-The discussion contains excessive narrative description and repetition of earlier findings. It would be a clearer comparison with key studies on ISUP upgrading rates. Correction has been made in Discussion and more recent studies were added in references.

9-While some references are recent, it would strengthen the manuscript to include more recent studies or systematic reviews to reinforce the findings and claims made in the discussion. Some recent studies were added in references.

10-Figure legend should be written more clearly. Correction has been made.

Associate Editor (1):
We thank you for your careful reading of the manuscript and your constructive remarks.

1- The abstract does not specify what constitutes “upgrading.”
Does any increase (e.g., ISUP 1 to 2) count, or only “significant” upgrading (e.g., ISUP 1 to ≥ 3)?
Define “upgrading” clearly in the Methods section.
The upgrading was defined in the abstract and is presented more clearly and completely in the methods section. It should be mentioned that ISUP Grade Group 1 is generally considered clinically insignificant, as it is typically asymptomatic and associated with a favorable prognosis. The remaining ISUP grades (ISUP > 1) are considered clinically significant.

2-Summary of Statistical analysis results should be mention in result section of ABSTRACT.
Correction has been made.

3-In the Results section, you state: “Age, PSA, PSA density (PSAD)… were not significantly associated with ISUP upgrading (P>0.05).”
However, in the next sentence, you state that ISUP Grade 1 on biopsy was significantly associated with upgrading (*P*=0.002 P=0.002).
Critique: “ISUP grade” is a pathological finding. You cannot say “pathological findings were not significant” and then list a pathological finding (ISUP 1) as significant. This is a contradiction.
Correction has been made.

4-The conclusion is somewhat generic. Instead of saying “should be taken into account,” specify how.
Corrections were made to the conclusion.

Kind regards,
Samaneh Esmaeili
Corresponding author

3 Revision 2

4 comments · 8 Jul 2026 – 22 Jul 2026

Referee 2 Reviewer

ACCEPT 8 Jul 2026

Dear Editor,
I have now read the revised version of the manuscript and the authors' response—the changes they made address the concerns I raised in the earlier round. The study design is now properly explained, the methodological gaps have been filled, and the reporting errors have been corrected. The limitations are discussed frankly, and the conclusions are appropriately measured for a retrospective study.
The paper reads much more clearly, and I believe the manuscript now meets the standard expected for NUM. I recommend acceptance.
Sincerely,

Referee 1 Reviewer

ACCEPT 8 Jul 2026

Dear AE,
All previously raised concerns regarding the manuscript have been satisfactorily addressed in the revised version.
The corrections have resolved the earlier issues, and the overall quality of the paper has improved significantly.
The manuscript now meets the scientific and editorial standards of the journal.

Associate Editor

ACCEPT 8 Jul 2026

Dear EIC,
Thank you for the invitation.
The reviewers and I have now completed the review process. We found this work to be of interest and suitable for publication pending major revisions.
The reviewers have provided constructive feedback to help improve the clarity and presentation of the manuscript. I encourage the authors to carefully address each of the reviewers' comments and submit a revised version of the manuscript.

Sincerely,
Associate Editor, Nephro-Urology Monthly

Editor-in-Chief

ACCEPT 22 Jul 2026

Dear Authors,
Your great effort in improving the manuscript is highly appreciated.
Now, it is acceptable.
Congratulations on your hard work and commitment to enhancing the quality of your research.